and 36) which were drawn to unelected inventions have been canceled.

Prior Art Issues

2. Claims 1, 2, and 4-18 were rejected as anticipated by one or more of eight cited references. Claims 3, 21-35, and 37 were not rejected over the prior art. In order to simplify the issues in this proceeding, claim 1 has been canceled, and claims 2 and 4-18 rewritten to depend from claim 3. It is therefore assumed that the claims, as amended, are free of the prior art, and applicants and the Examiner may devote their attention to the remaining issues.

Claim Definiteness

3. The claims have been amended to overcome the indefiniteness rejections, as indicated below.

3.1 Claim 9 has been amended to depend from claim 3.

3.2 Those of claims 21-35 which refer to "pediatric immunization" of a "mammal" have been amended to delete "pediatric", in deference to the Examiner's view that "pediatric" refers strictly to human children. However, Applicant wishes to state for the record that pediatrics is also a branch of veterinary medicine, and that the amendment has been made only because, in Applicant's view, this amendment does not affect the substantive scope of these claims (which contain explicit age limitations).

3.3 The Examiner's criticism of claim 22 lacks antecedent basis in claim 21 for the term "said mammal of at least 28 days of age but less than 175 days of age" has been met by amending claim 22 by inserting a comma after "said mammal" (thereby limiting what was asserted to have been said before to the word "mammal"), and inserting --at-- after that comma.

3.4 With regard to the awkward phrase "said at least one dose comprises a total of at least four separate doses", the

deletion of the "one dose" phrase should clarify the intended subject matter.

Enablement

4. The Examiner concedes that the disclosure is enabling for NOD mice immunized with (a) "anthrax or plague vaccine at days 8, 15 and 29 of life", (b) a combination of anthrax, diphtheria and tetanus vaccines, or (c) a combination "combined whole cell pertussis diphtheria tetanus vaccine", to "reduce the" incidence or severity of at least one chronic immune-mediated disorder", especially the incidence of diabetes mellitus. However, the Examiner questions the utility of the disclosed methodology in other mammals (especially humans), against other chronic immune-mediated disorders, and using other immunogens or dosage schedules than those set forth in the Examples, and therefore objects to the specification and rejects claims 1-18, 21-35 and 37. The objection and rejections under 35 U.S.C. §112, first paragraph are respectfully traversed.

4.1 *Extrapolatability to Humans.* It is well settled that animal data (or even in vitro data) can establish the utility of a therapeutic method in humans if there is an accepted correlation between efficacy in the animal in question, and efficacy in humans. See In re Jolles, 206 USPQ 885 (CCPA 1980); Nelson v. Bowley, 206 USPQ 881 (CCPA 1980); Cross v. Iizuka, 224 USPQ 739 (Fed. Cir. 1985). The law does not requires that this correlation be perfect, merely that it give the researcher a reasonable expectation that a drug which does well in animal testing will be successful in humans.

The expectation exists here because:

(1) the specification establishes efficacy in NOD mice, and NOD mice are an accepted animal model of diabetes mellitus in humans;

(2) the method of the present invention was effective in a second species of animals, BB rats, which are likewise accepted as animal models of human diabetes mellitus; and

(3) the utility of the present invention in humans is made more believable by human epidemiological data.

4.1.1 It is now widely accepted by those skilled in the art that type I diabetes in humans responds similarly to immune intervention as does diabetes in NOD mice and BB rats. Diabetes in all three species is considered to be an autoimmune disease based on the presence of islet cell autoantibodies and strong genetic linkage between the development of diabetes and MHC genes (New England Journal of Medicine 314:1360-1368,1986; Diabetes Reviews 1:15-42,1993). Immunological events occurring in the first 2 months of life have been clearly shown to be responsible for the development of diabetes in NOD mice and BB rats. Similarly, recent human epidemiology data shows that immunological events occurring at birth have a profound effect on the development of human diabetes. These events include maternal fetal blood group incompatibility as well as exposure to rubella virus and nitrates at birth (Diabetes Reviews 1:15-42,1993; Diabetologia 35:671-765,1992).

The concept of diabetes in humans responding similarly to diabetes in NOD mice is widely accepted. This has been justified by therapeutic experience. Clinical trials have shown that type I diabetes in humans can be prevented by immunosuppressants like cyclosporine when administered to prediabetics or newly diagnosed diabetics (Diabetes Reviews 1:15-42,1993). Immunosuppressants have a similar effect on NOD mice and BB rats (Clinical and Investigative Medicine 10:488-495,1987). The NIH recently embarked on a trial of screening up to 80,000 children to initiate a program of treating prediabetics with insulin immunotherapy, after a small phase I trial in humans supported results developed in NOD mice (Lancet 341:927-928,1993).

By reason of these findings, the art has often recognized the value of NOD mice and BB rats as models for diabetes in humans and has used these models to evaluate anti-diabetic therapies. The following citations illustrate the degree of acceptance these models have earned:

i) "Thus, clinical and pathological features in the NOD mouse closely resemble human type 1 (insulin dependent) diabetes mellitus." (Lampeter, Signore, Gale, and Pozzilli, Diabetologia 32:703-708, 1989; from page 703 paragraph 1 line 11)

ii) "Insulin-dependent diabetes mellitus (IDDM) is strikingly similar in the non-obese (NOD) mouse and humans" (Pacheo-Silva, Bastos, Muggia, Pankewez, Nichols, Murphy, Strom, and Rubbin-Kelley, Eur.J. Immunology 22:697-702,1992; from page 697 line 1)

iii) "Inaccessibility of the affected organ, inability to conduct prospective genetic studies, and ethical constraints on human subject research all limit the study of IDDM. For these reasons investigators have turned to animal models of the disorder. Despite the constraints of modeled systems, they have provided useful insights into the pathogenesis of the disease process. Animal models with reasonable analogy to human IDDM and a probable autoimmune pathogenesis include BB rat and the non-obese diabetic (NOD) mouse" (Rossini, Handler, Greiner, and Mordes, Autoimmunity 18:221-225,1991; from page 222 column 2 last paragraph line 4)

iv) "There is a growing interest in using NOD mice for evaluation of immune intervention protocols that might be considered in the human disease. The observation of a preventive effect of nicotinamide (see below) already has led with this substance in humans." (Kolb, Diabetes/Metabolism Reviews 3:751-758,1987; from page 765 line 34).

v) "The BB rat, NOD mouse, and other animal models have provided valuable information on the possible immunopathogenic

mechanisms responsible for human IDDM". (IBID page 229 line 36)

vi) "The NOD mouse is an ideal model of organ specific autoimmune disease as well as IDDM" (Kikutani and Makino, Advances in Immunology 51: 285-321,1992; from page 310 line 27)

vii) "The nonobese diabetic (NOD) mouse strain provides a model system for human autoimmune diabetes. This disease model is extensively used not only to examine the etiology and pathogenesis of diabetes , but also as a means to evaluate therapies." (Fox, J.Exp.Med. 175:1409-1412,1992;from page 1409, summary line 1)

viii) "The inbred nonobese diabetic (NOD) mouse spontaneously develops an autoimmune diabetes, which is now recognized as an experimental model for human insulin-dependent diabetes mellitus." (Fitzpatrick, Lepault, Homo-Delarche, Bach, and Dardene, Endocrinology 129:1382-1390, 1991; page 1382 column 1 line 1.)

ix) "The nonobese diabetic (NOD) mouse strain described originally by Maiko et al. develops diabetes spontaneously and is considered a good model for autoimmune insulin-dependent diabetes mellitus." (Hawkins, Gala, and Dunbar P.S.E.B.M. 202:201-205,1993; from page 201 column 1 line 1)

x) "Nonobese diabetic (NOD) mice spontaneously develop diabetes remarkably similar to human autoimmune insulin dependent diabetes mellitus" (Jacob, Aiso, Michie, Mcdevitt,and Acha-Obea; Proc. National Acad.Sci.USA 87:968-972, 1990; page 968 column 1 first line first paragraph)

xi) "The nonobese diabetic mouse (NOD) is considered to be an animal model suitable for studying the pathogenesis of human autoimmune insulin-dependent diabetes mellitus" (McInerney, Pek and Thomas, Diabetes 40:715-725,1991; Page 715 column 2 line 1)

xii) "The nonobese diabetic (NOD) mouse, an animal model of spontaneous diabetes, shares many features with human

insulin-dependent diabetes mellitus (IDDM), including the abrupt onset of overt diabetes, the dependance of exogenous insulin to sustain life, the presence of lymphocytic infiltration of islet cells before the onset of hyperglycemia, and prevention of disease by immunotherapy" (Karounos and Thomas, Diabetes 39:1085-1090,1990; page 1085 column 1 first paragraph line 1).

xiii) "The spontaneously diabetic BB rat is an excellent laboratory 'model' of type I (insulin dependent juvenile onset) diabetes mellitus, with both metabolic and immunological defects." (Yale and Marliss, Cln.Exp.Immunol 57:1-11,1984; page 1 introduction line 1)

xiv) "The availability of two excellent animal models for type I diabetes mellitus promises to lead to a better understanding of genetic mechanisms which can cause the autoimmune destruction of the beta cells in the pancreatic islets of Langerhans. In the nonobese diabetic (NOD) mouse,..." (Kastern ,Lang and Sorensen, Current Topics in Microbiology and Immunology 156:87-102, 1990; page 87 paragraph 2 line 1)

xv) "Insulin-dependent diabetes mellitus (IDDM) is an organ-specific autoimmune disease. The NOD mouse is an excellent animal model of human IDDM." (Wang,Singh,Warnok,and Rajotte, Diabetes 41:114-117,1992; page 114 column 2 line 1)

xvi) "Type I diabetes is known to occur in three different species: man, nonobese diabetic (NOD) mouse and Bio Breeding (BB) rat." (Dotta and Eisenbarth, Clinical Immunology and Immunopathology 50:S85-S95,1989; Page S86 paragraph 2 line 1).

xvii) "Insulin-dependent diabetes (IDDM) of both humans and NOD strain mice becomes clinically overt after most of the beta cells in the islets have been destroyed by an autoimmune process." (Elias, Reshef,Birk, van der Zee, Walker, Cohen, Proc. Natl. Acad. Sci. 88:3088-3091, 1991; page 3088 column 1 paragraph 1).

xviii) "One may reasonably ask if data obtained in rat models apply to humans. The answer is a qualified yes. For example, human clinical trials using cyclosporin were begun after successful use in the BB rat." (Rossini, Mordes, and Like, Ann Rev. Immunolog. 3:289-320,1985; from page 310 line 33).

As described in the attached Declaration, diabetes prone BB rats were immunized according to the method disclosed in the specification in order to show that the method of immunization could prevent diabetes in other species beside NOD mice.

BB rats spontaneously develop diabetes at an early age as is the case in NOD mice and humans. Many of the findings present in human type I diabetics and in NOD mice are found in BB rats leading experts to believe diabetes in BB rats is also a autoimmune disorder. Insulitis develops in the pancreas of BB rats before the onset of diabetes while antibodies develop to islet cells and possibly to insulin. Diabetes can be prevented by neonatal thymectomy as well as administration during the prediabetic period of cyclosporine, anti-lymphocyte antibodies, or purified lymphokines like TNF. Genetic experiments show that diabetes is closely linked to the MHC class II genes in BB rat as it is in humans. Many older rats develop autoimmune thyroiditis that is casually related to the development of diabetes as occurs in humans.

BB rats have an immunologically distinct disease from the disease in NOD mice. Diabetes develops in approximately equal numbers of males and females in contrast to NOD mice where disease develops more commonly in females. The incidence of diabetes in BB rats is not affected by gonadectomy or the administration of androgens as occurs with NOD mice. In contrast to humans and NOD mice, BB/Wor rats, the most commonly used substrain of BB rats, are severely lymphogenic. They have a marked decreased number of mature T lymphocytes in peripheral blood, spleen and lymph nodes. The CD4+ subset

is substantially reduced but the CD8+ subset is almost completely absent. Natural killer cells are relatively over expressed. Several review papers have been published on this model (Diabetes and Metabolism Reviews, 8: 9-37;1992).

BB rats were immunized with a combination of the anthrax and DTP vaccines (n=20) or nothing as a control (n=28). Groups contained approximately equal number of male and female rats. The vaccinated group was given the following dosing schedule: day 1 (.1ml,1:5); day 4 (.15ml, 1:5), day 11 (.15ml, 1:5), day 25 (.2ml, 1:5), day 39 (.2ml, 1:5), day 53 (.2ml, 1:5), day 61 (.2ml 1:2.5), and every 14 days for 3 more injections at approximately (.2ml, 1:2.5). Days of injection varied by one at times. The notation 1:5 means 1 part vaccine to 5 parts PBS. At 16 weeks of age 54% of the untreated rats had developed diabetes and or died compared to 20% in the vaccinated group. At 20 weeks of age 54% of the untreated rats had developed diabetes and or died compared to 25% in the vaccinated group. At 32 weeks the results were 54% versus 35% respectively (graph I) which represents a 34% reduction in the incidence of diabetes. The difference between the two groups were statistically significant at 20 weeks (P=0.027). The findings that the method of immunization can prevent diabetes in both NOD mice and BB rats provides strong proof that methods of immunization presented in the specification have the ability to prevent chronic immune mediated diseases in mammals with very different genetic defects.

4.1.2 An epidemiology study described in example 4 of the specification (page 82 line 17, page 84, line 21) showed that the incidence of diabetes in western European countries was closely correlated with a country's vaccination schedule. Europe was chosen because in a relatively small geographic area there are many different countries that have different immunization schedules and the incidence of diabetes in the countries is known. The people in the western European countries have closely related racial backgrounds, diets,

economic standards of living, and standards of health care. Eastern European countries of the former communist block were excluded because their standard of living and standard of medical care is not up to western levels.

The data correlating the incidence of diabetes to immunization schedule in western European countries is presented in Table 1, attached hereto. Several additional countries are included in Table 1 that were not included in example 4 of the specifications because the new data was collected after the patent was applied for.

The data in Table 1 substantiates the previous findings presented in example 4 (page 82) of the specification. Administration of vaccines after 2 months increases the incidence of diabetes while administration of vaccines at birth can prevent diabetes. The findings are highly statistically significant. Administration of the pertussis vaccine after 2 month of age explains the higher incidence of diabetes in group 3 compared to most regions in group 1. Administration of the BCG vaccine after 2 months of age explains the higher incidence of diabetes in Group 4 compared to group 3. Administration of the Hemophilus influenza vaccine after 2 months of age explains the higher incidence of diabetes in group 5 compared to 4. The ability of the BCG vaccine to protect against diabetes when administered at birth explains the lower incidence of diabetes in group 2 compared to most regions in group 3.

Further details are provided in the Classen Declaration. Temporal studies were done to show the incidence of diabetes changed in a rational way after the immunization schedule changed. Published reports, showing that diabetes in humans can be caused by transient immune disturbances at birth, are also discussed.

The epidemiological data presented above is evidence of efficacy in humans. In re Irons, 144 USPQ 351 (CCPA 1965)

held that "historical" data could be used to establish utility.

4.2 *Efficacy Against Other Chronic Immune-Mediated Disorders.* The Examiner doubts the ability of a person of ordinary skill to adapt the teachings of the present invention to a chronic immune mediated disorder (as defined at pages 35-38 of the specification) other than diabetes. Her doubts appear to be primarily founded on the assumption that an equal and considerable amount of time would have to be devoted to each of a large (though a hypothetical) number of such disorders ("perhaps hundreds or thousands of diseases ranging from hay fever to cancer").

4.2.1 However, it is well settled that the number of embodiments embraced by a claim is not the best measure of the difficulty of practicing it without undue experimentation. Disorders which are manifested through a common mechanism are likely to have a common cure or palliative. For example, a patient suffering from an allergic response may be given an antihistamine, regardless of the nature of the allergen. A particular immunosuppressant may be useful for treating a variety of autoimmune diseases.

4.2.2 Many patents have been issued which claim treatment of a large class of diseases while only showing examples of treating a single disease. In the field of autoimmune diseases, the following patents come to mind:

i) U.S. patent 4,695,459 claim 3 (column 6 line 45) claims a method of treating multiple diseases in humans including multiple sclerosis, systemic lupus erythematosus, psoriasis, juvenile onset diabetes, Sjorgren's disease, thyroid disease, or myasthenia gravis. The specification only gave an example of treating EAE in mice.

ii) U.S. patent 4,710,380 claim 1 (column 5 line 47) claims a method of treating human or mammal subjects for "disorders characterized by an hyperactive immune response". The term is similar to the term chronic immune mediated

disorders used in our application because both encompasses rheumatoid arthritis, lupus, type I diabetes, and other autoimmune disorders (page 36 line 8). Patent 4, 710,380 contains only examples of rheumatoid arthritis patients being treated with its claimed method, however, its claim 1 encompasses all hyperactive immune responses.

4.2.3 In paragraph 4 of the Classen Declaration, data is presented which shows that the method of the present invention inhibits spontaneous autoimmunity in MRL/1pr mice. These mice, absent intervention, develop a disease which closely resembles the autoimmune disorder Systemic Lupus Erythematosis (SLE) in humans. Like SLE patients, the MRL/1Pr mice develop anti-DNA and anti-nuclear autoantibodies which can form immune complexes, which in turn can cause arthritis, dermatitis, and glomerulonephritis.

The MRL data is important not only because it is a good model for human SLE but because this autoimmune disease is both genetically, immunologically, and clinically very different from diabetes. The following are a few references verifying both the similarity of the disease in MRL mice to SLE in humans and the clinical importance of the MRL model.

i. "MRL/l mice develop progressive, virulent autoimmune disease that has many of the features of systemic lupus erythematous...The MRL/l mouse model of systemic lupus erythematous provides, an experimental system that permits exploration of the effect of T-cell directed therapeutic maneuvers on the course of autoimmune disease. "(Berger, Perez, Laroche, Edelson 1990, J. Investigative Dermatology 94:52-57.)

ii. "The MRL-lpr/lpr strain of mouse spontaneously develops an autoimmune disease that closely resembles the human disease systemic lupus erythematous (SLE)." (Halpern, Hersh, Yocum 1990, Clinical Immunology and Immunopathology 55:242-254)

iii. "Murine Models of systemic lupus erythematous (SLE) have contributed significantly to our understanding of human

autoimmunity. Most of the immunologic abnormalities of the human disease are also present in mouse models. One of these models, the MRL/lpr-lpr ..." (Guitierrez-ramos, Andreu, Marcos, Vegazo, and Martinez 1991, Autoimmunity 10:15-25)

iv. "Although the MRL/lpr syndrome is different from human SLE in that the lpr gene causes proliferation of an unusual subset of T-Cells, MRL/lpr disease is strikingly similar in a number of aspects to human disease." (Shlomchick, Mascelli, Shan, Radic et al. 1990; J.Exp. Medicine 171:265-297)

v."The MRL-lpr/lpr mouse, a genetic model of the human autoimmune disease systemic lupus erythematosus, has been studied extensively to determine the etiology and the pathological course of the disease in lymphoid organs" (Breneman, Moynihan, Grota, Felten, Felten 1993; Brain, Behavior, & Immunity 7:135-43)

vi."MRL/lpr and MRL/+ autoimmune mice thus provide unique models for human SLE, because they express several of the SLE-specific marker autoantibodies. These models should be useful in disclosing molecular and immunologic events governing autoantibody expression in this condition. (Treadwell, Cohen, Williams, O'Brien, Volkman, Eisenberg 1993; Journal of Immunology 150:695-9.

vii."These results suggest a beneficial role of 1,25-D3 in the prevention or attenuation of some manifestations of murine SLE, a model sharing many immunologic features with human SLE."(Lemire, Ince, Takashima 1992, Autoimmunity 12:143-8.)

viii."The MRL-lpr murine model of systemic lupus erythematosus (SLE) has provided many insights into the pathology of human lupus."(Gallina, Steele 1991; Journal of Autoimmunity, 4:755-68)

ix."The classical types of generalized autoimmune disease in man are systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Several murine strains which develop SLE and sometimes RA-like diseases are now available. They should help in the understanding of the etiopathology of SLE and RA...This

paper reviews the data published about NZB, NZB/W, BXSB and MRL mice in this context." (Loor, Jachez, Montecino-Rodriguez, Klein, Kuntz, et al. 1988; International Journal of Radiation Biology & Related Studies in Physics, Chemistry & Medicine, 53:119-36.)

x." MRL/lpr mice spontaneously develop a systemic Lupus erythematosus (SLE)-like disease with a wide range of clinical and serological characteristics that mimic not only human SLE but other autoimmune disorders such as Sjogren's syndrome, and rheumatoid arthritis (RA).(Bartlett, Popovic, Raiss 1988; Scandinavian Journal of Rheumatology - Supplement. 75:290-9, 1988.)

xi."MRL-+, MRL-lpr and B6-lpr have been shown to be useful models in studying systemic lupus erythematosus."(Waterfield, Fairhurst, Chu, Levy, 1987; Immunology 61:173-8.)

As described in the declaration, MRL/MpJ-lpr mice were injected either with a control (PBS) or with the anthrax/DTP combination, following an immunization schedule within the teachings of the present invention. At 15 weeks, 26.3% control mice exhibited significant proteinuria (an accepted sign of glomerulonephritis), while only 7.7% of the vaccinated mice developed comparable levels of protein in their urine.

4.2.4 Even if the Examiner still does not believe that the disclosure is enabling for all chronic immune-mediated disorders, she is invited to consider whether the limitation of claim 15 is acceptable:

> A method according to claim 1, wherein said chronic immune mediated disorder is selected from the group consisting of an autoimmune disease, asthma/allergy, and an immune mediated cancer.

4.3 *Choice of Immunogen*. While the experimental example in the specification related to use of anthrax (Ex. 1) plague (Ex. 1), anthrax + diphtheria + tetanus (ADT) (Ex. 2), and anthrax + DPT (Ex. 2), numerous additional immunogens are disclosed at pages 24-25 of the specification. Since both

disclosed at pages 24-25 of the specification. Since both anthrax and plague immunogens were effective, though immunologically unrelated, the Examiner does not have reasonable basis for doubting that additional immunogens could be effective.

At page 56-76 of the specification, Applicant discusses, in great detail, methods of identifying immunogens suitable for the present invention. As explained in paragraph 5 of the Declaration, the epidemiology data set forth in the specification and Declaration indicate that many immunogens mediate the development of diabetes.

To the extent that occasional immunogens are ineffective, they are excluded by the functional limitations of claim 3 (per base claim 1). A "biological activity" limitation was given weight, in a finding that a generic claim to a cysteine-depleted mutein was enabled, in Ex parte Mark, 12 USPQ2d 1904 (POBA 1989).

4.4 *Immunization Schedule*. Claim 1 requires that the first dose of the immunization schedule be given before 42 days after birth.

In the "Summary of the Invention (page 12, line 26 - page 13 line 1) one skilled in the art is instructed that "the immunization schedules of the present invention may include employing initiating immunization prior to 28 days, supraimmunogenic doses, multiple doses prior to 56 or 112 days, and/or dosing intervals less than 28 days." In the "Detailed Description of the Preferred Embodiments" (page 56, line 3-10), the worker in the art is told: "In a preferred embodiment, an immunogen designed to reduce the incidence of a chronic immune-mediated disorder can be given starting during the first week of life and continuing as frequently as practically possible and safe to do so for at least the first 8 to 32 weeks.

One skilled in the art would know the limitations of immunizing humans and would be able to design an vaccination

schedule to perform the intended function. The frequency of immunization is limited by the frequency that individuals are willing to have a health official vaccinate their children. In Belgium in the 1960s, well baby care involved bringing the child to the doctor every 2 weeks until the child was 8 weeks old J. Royal College of General Practitioners 24:676-686, 1974). This is almost the identical schedule as used to immunize diabetic prone mice in example 2 (page 79, line 1).

At page 56, lines 17-26, the specification continues:.

> Vaccination schedules can be as short as 3 shots and as infrequent as every other week and still be effective. Example 1, as non-limiting example, shows that only 3 vaccinations with a single mild agent, anthrax vaccine, can cause a profound reduction in diabetes. Increasing the number of vaccination increases the effect when using a mild agent like the anthrax vaccine as seen by the improvement from Example 1 to Example 2. Even fewer injections or less frequent injection protocols may also be used, especially when using a strong agent like the DTP vaccine or higher doses.

In Example 1, the NOD mice received anthrax vaccine on days 8, 15 and 29 of life (after birth). This was a three dose schedule, and it was effective against diabetes.

In Example 2, the immunization schedule was changed to a nine dose one: day 1, day 3, day 10, and weeks 4, 6, 8, 10, 12 and 14. This schedule was also effective, although it started earlier, ended later, and involved more doses than that of Example 3.

Additional schedules were used successfully in Example 3: (a) day 10, day 17, and every 2 weeks for 2 more injections; and (b) day 6-8, day 14-16 and day 27-29.

It is respectfully urged that with the guidance of the recommendations and examples in the specification, a person of ordinary skill in the art can develop a safe and effective immunization schedule without undue experimentation. This

conclusion is confirmed by paragraph 6 of the Classen Declaration.

Respectfully submitted,

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